

Application No. 10/006,593

Docket No.: ALEX-P01-054

REMARKS

Claims 1-3, 5-11, 18-23, 36, 44, 85-87, 89, and 96-126 constitute the pending claims in the present application.

Claim Objections and Amendments

Claims 113-126 were objected to on the basis that the status identifiers were not updated to “previously presented.” Applicants note that claims 113-126 were added in association with the Response and Amendment dated April 19, 2007. The claims were not amended in the Response filed January 22, 2008 and therefore Applicants believed that there was no obligation to update the status identifiers in that Response. The status identifiers are updated in the present Amendment. The only amendments presented are to claims 123 and 126 wherein the word “molecule” is added to each claim solely to keep the claim language consistent throughout claims 113-126.

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-11, 18-19, 22-23, 36, 44, 85-87, 89, and 96-126 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. The Office Action asserts that the claims are drawn to an immunoglobulin molecule and that the structure of an immunoglobulin molecule is defined by the presence of six CDR regions in a particular arrangement to function in binding antigen. The Office Action further asserts the necessity of all six CDRs for maintaining the function of an immunoglobulin molecule to bind antigen. Finally, the Office Action asserts that references of Rudikoff et al., Colman et al., and Ibragimova et al. are relevant to the structure and function of an immunoglobulin molecule. Applicants respectfully traverse.

Applicants wish to draw the Examiner’s attention to related application USSN 10/307,724 (the ‘724 application) which issued as US Patent No. 7,396,917 on July 8, 2008. The ‘724 application is a continuation-in-part of the instant application and contains claims directed to, for example, an immunoglobulin molecule or fragment thereof comprising at least two peptide mimetics replacing portions of at least two complementarity determining regions (CDRs), wherein the immunoglobulin molecule or fragment thereof binds to and agonizes a receptor. Applicants note that the Pre-Appeal Conference on the issue of enablement was decided in Applicants’ favor. The Notice of Allowance issued on February 25, 2008 states that “[t]he working examples clearly show

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that the peptide mimetics may be inserted in the combinations of heavy and light chain CDR portions as shown in Tables 1 and 2, and in each case result in an immunoglobulin molecule that acts as an agonist.”

Applicants note that instant claims are not directed to an “immunoglobulin molecule or fragment thereof.” Rather the claims are directed to an immunoglobulin molecule or fragment thereof *wherein a portion of a CDR has been replaced with a peptide*, such as an agonist peptide or a biologically active peptide, and the molecule *exhibits the activity of the peptide* incorporated into the immunoglobulin molecule or fragment thereof.

As explained in the previous response (dated January 22, 2008), the binding ability of the claimed immunoglobulin molecules does not depend on the precise three dimensional conformation of the CDR regions as is the case for conventional antibody-antigen interactions. The peptide mimetics are inserted into the CDRs only because these regions are solvent exposed. As opposed to a typical antibody wherein it is necessary for the six different CDRs to be in the proper conformation relative to each other for proper binding to the antibody target and where a change in the antibody sequence may disrupt the normal conformation, in the present case the immunoglobulin is acting as a *carrier for a peptide* and it is merely necessary for the peptide mimetic within the carrier to be exposed and to retain its activity, the remaining 5 CDRs are irrelevant. There is no need for six separate CDRs to bind a single target in the claimed molecules, rather the peptide mimetic only needs to bind the target. The CDR sequence that is being replaced by the mimetic is irrelevant to the activity of the mimetic.

The Examples provided in the application clearly demonstrate that the immunoglobulin is acting as a carrier for a peptide rather than acting as a conventional antibody. In particular, Example 1 involves grafting of a TPO mimetic into the HCDR3 region of an anti-tetanus toxoid (anti-TT) Fab. The original anti-TT Fab and several anti-TT Fabs having a TPO mimetic inserted into the HCDR3 region were tested for binding to the original antigen. The specification shows that the anti-TT Fab bound to its antigen TT but did not bind to BSA (e.g., the binding of the unmodified anti-TT Fab was specific for its antigen). However, the four TPO-mimetic peptide grafted clones did not show significant binding to TT or BSA. (See page 43, lines 17-22 of the instant application.) In addition, anti-TT Fabs containing a TPO mimetic inserted into the HCDR3 region demonstrated strong binding to cells transfected with cMpl-R, the TPO receptor, but did not bind to

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control cells not expressing cMpl-R. The original anti-TT Fab does not bind to control cells or cells transfected with cMpl-R. (See page 44, lines 8-14 of the instant application.) Therefore, replacement of anti-TT Fab HCDR3 with a TPO mimetic was sufficient to change the binding specificity of the Fab. Furthermore, the specification clearly demonstrates that the anti-TT Fabs containing a TPO mimetic in the HCDR3 region could bind to the TPO receptor and activate the receptor. (See e.g., Example 1 starting at page 40, especially the section labeled "Biological Assays" on page 46, line 3 through the Table on page 47.) Accordingly, the specification clearly demonstrates that the immunoglobulin referred to in the instant claims is acting as a carrier rather than a conventional antibody and therefore clearly enables the claimed molecules.

The working examples clearly demonstrate that peptide mimetics may be inserted into a variety of CDRs, e.g., HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, and in each case result in immunoglobulins that exhibit the biological activity of the introduced peptide mimetic. This is in sharp contrast to conventional antibodies where amino acid sequences cannot be swapped between CDR regions. Further, the lengths of the peptide mimetics are not necessarily the same as the CDRs which they replace. For example, Examples 2 and 3 teach the replacement of HCDR2 or HCDR3 together with LCDR1, LCDR2 or LCDR3. The TPO mimetic being inserted is 14 amino acids and flanking regions are also included. The CDR regions being replaced with the TPO mimetic are of varying lengths: HCDR2 is 17 amino acids, HCDR3 is 16 amino acids, LCDR1 is 12 amino acids, LCDR2 is 7 amino acids, and LCDR3 is 8 amino acids. This demonstrates that there is not a strict size limitation on the mimetic being inserted. The results of the working examples demonstrate that *the claimed molecules are not subject to the same structural requirements as conventional antibodies*. As noted previously, this is due to a different mechanism of binding the desired target. Therefore, the Office Action is incorrect in the assertion that the structural integrity of the CDRs is important for the functionality of such immunoglobulin molecules. The presently claimed immunoglobulin molecules are merely carriers for peptide mimetics that are inserted into solvent exposed CDRs; they are not meant to act as conventional immunoglobulins.

Applicants respectfully disagree with the Examiner's reliance on the Rudikoff et al., Colman et al., Ibragimova and Wade references. While these references may be relevant to the structure and function of immunoglobulin molecules, they clearly are not relevant to the claimed molecules.

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Rudikoff et al. is relied on for teaching that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. This is irrelevant. What Rudikoff teaches are antibodies that bind to specific antigens. This binding specificity is determined by the 6 CDRs. Changing the sequence of a CDR would not surprisingly interfere with the ability of the antibody to properly bind its target antigen. It is after all those amino acids in the CDRs that need to interact with the target antigen. In the present application it must be noted that the peptide mimetics being inserted into the CDR regions always retain their complete sequence, i.e., no changes are being made to the peptide mimetic sequence itself. Therefore there is no reason to assume that the peptide mimetic will lose its activity.

The Colman publication mostly does not discuss its findings in terms of CDRs or frameworks, but it does seem to be discussing amino acid substitution in "antibody-antigen interfaces." Again, it is the CDRs which tend to directly contact the target and thus will be at the antibody-antigen interface and as already noted, changes in CDRs themselves can be expected to affect binding. But to repeat the point above, the inserted peptide mimetics are being inserted without any changes to the mimetics and thus there is no reason to believe that they will lose their mimetic activity.

Concerning the Ibragimova and Wade publication, Applicants do not disagree that small changes may affect the folding of a protein. But as previously discussed, an antibody acting as a normal antibody (e.g., binding antigen) is required to properly fold such that 6 separate CDRs will all appropriately contact the antigen.

In contrast to the cited references which are directed to antibodies having antigen binding function, the claimed molecules do not function as immunoglobulins, e.g., they do not bind antigen. For the claimed molecules, one is only concerned with a single short region (e.g., the introduced peptide) and there is no need for exquisitely proper folding to enable 6 separate regions to be in their proper 3-dimensional positions. All that is required is for the single peptide to be in a position such that it is exposed and can carry out its biological activity, such as interacting with a target receptor. Thus the claimed molecules should be able to tolerate a lot of change to the overall structure of the immunoglobulin without losing the desired biological activity.

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Accordingly, Applicants submit that the pending claims clearly meet the enablement requirements under 35 USC §112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 1-3, 5-8, 18, 22, 23, 36, 44, 85, and 97-112 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 11, 16, 26-35, and 38-56 of copending Application No. 10/307,724. Applicants submit herewith a terminal disclaimer. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSIONS

In view of the above remarks, Applicants believe the pending application is in condition for allowance. Applicants believe no fee is due other than those itemized on the enclosed transmittal. However, should an additional fee be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 18-1945, from which the undersigned is authorized to draw under ALEX-P01-054.

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Respectfully submitted,

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